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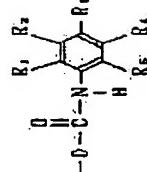
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(54) SUBSTITUTED AROMATIC CARBAMATE DERIVATIVE OF POLYSACCHARIDE, AND
 SEPARATING AGENT

(57)Abstract:

PURPOSE: To obtain a compd. useful as the active ingredient of a separating agent usable in separation of various chemical substances, particularly in optical resolution, by choosing a substid. arom. carbamate deriv. of a polysaccharide having a predetermined amt. of the OH groups thereof substid. with specific groups.

CONSTITUTION: Choice is made of a substid. arom. carbamate deriv. of a polysaccharide (e.g. cellulose) having 80-100% of the OH groups thereof substid. with groups of the formula (wherein R1 to R4 are each H, 1-8C alkyl, or a halogen atom, provided that at least two of R1 to R4 are each 1-8C alkyl or a halogen atom, and are different from each other).



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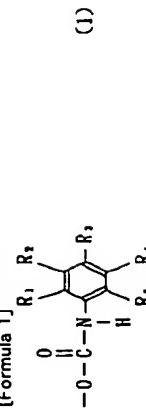
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CLAIMS

[Claim(s)]

[Claim 1] ** [80% of the hydroxyl group which a polysaccharide has cannot be found] 100% is the following general formula (1). Permutation aromatic series carbamate derivative of the polysaccharide permuted by the radical shown.



(R1, R2, R3, and R4 and R5 are a **** atom or a carbon number 1 thru/or eight alkyl groups, or a halogen atom among a formula, respectively, and at least two of R1-R5 are a carbon number 1 thru/or the alkyl group of 8 or a halogen atom, and it is a different substituent.)

[Claim 2] General formula (1) Permutation aromatic series carbamate derivative of the polysaccharide according to claim 1 whose at least one it sets, and at least one of R1-R5 is a carbon number 1 thru/or the alkyl group of 8, and is a halogen atom.

[Claim 3] The separating medium which makes an active principle the permutation aromatic series carbamate derivative of a polysaccharide according to claim 1.

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DETAILED DESCRIPTION

[Detailed Description of the Invention]

[0001]

[Industrial Application] This invention relates to the separating medium which makes an active principle a very useful new polysaccharide derivative and this polysaccharide derivative as a functional material. The separating medium of this invention can be used for separation of various chemicals, especially optical resolution.

[0002]

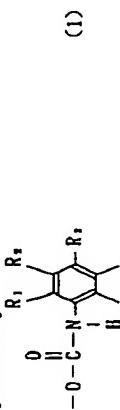
[Description of the Prior Art] Even if it is the same compound chemically as known well, the optical isomer usually differs in the operation to a living body. Therefore, in fields, such as physical, agricultural chemicals, and a biochemistry related industry, it has been very important technical problem to prepare a pure compound optically for improvement in the drug effect per unit, prevention of a side effect and phototoxicity, etc. By current, the mixture of an optical isomer has been studied about the optical-resolution ability of many polysaccharide derivatives, separation, i.e., in order to carry out optical resolution. For example, cellulose tris phenyl carbamate (J.Am.Chem.Soc., 106, 5357, 1984) Having the optical-resolution ability excellent in the bulking agent for liquid chromatography which makes a stationary phase the alkylation phenyl carbamate derivatives (JP-63-178101A, JP-1-203402A, etc.) of a polysaccharide and the halogenation aromatic series carbamate derivative (JP-61-233633A) of a polysaccharide is already known. However, it is a fact that there is a compound which cannot carry out optical resolution even if it uses these polysaccharides derivative, and development of the separating medium which can carry out optical resolution also of such a compound is desired.

[0003]

[Means for Solving the Problem] This invention person etc. came to complete a header and this invention for having the dissymmetry discernment ability excellent in the carbamate derivative of the polysaccharide which has the aromatic series radical which has two or more kinds of different substituents, as a result of advancing research wholeheartedly in order to solve such a technical problem. That is, this invention is ** [80% of the hydroxyl group which a polysaccharide has cannot be found]. 100% is the following general formula (1). The separating medium which makes an active principle the permutation aromatic series carbamate derivative of the polysaccharide permuted by the radical shown and the permutation aromatic series carbamate derivative of this polysaccharide is offered.

[0004]

[Formula 2]



[0005] (R1, R2, R3, and R4 and R5 are a *** atom or a carbon number 1 thru/or eight alkyl)

groups, or a halogen atom among a formula, respectively.) At least two of R1-R5 are a carbon number 1 thru/or the alkyl group of 8, or a halogen atom, and they are a different substituent. It does not ask any of a synthetic polysaccharide, a natural polysaccharide, and a natural conversion polysaccharide they are, but although what kind of thing is sufficient as it as long as the polysaccharide in this invention is optical activity, its desirable regularity of a joint format is high. If it illustrates — beta-1, 4-glucan (cellulose), alpha-1, and 4-glucan (an amylose —>) An amylopectin, alpha-1, 6-glucan, beta-1, 6-glucan (BUSUTSURAN), alpha-1, 6-glucan, beta-1, 3-glucan, beta-1, 3-glucan (for example, curdlan, sizofiran, etc.), alpha-1, 3-glucan, beta-1, 6-mannan, alpha-1, 6-mannan, beta-1, 2-cell tongue (inulin), beta-2, 6-cell tongue (levan), it is beta-1, 4-xylan, beta-1, 4-chitosan, beta-1, 4-N-acetyl chitosan (chitin), a pullulan, agarose, an algic acid, etc., and the starch containing an amylose etc. is contained. Especially desirable things are beta-1 which can obtain the polysaccharide of a high grade easily. 4-glucan (cellulose), alpha-1, 4-glucan (an amylose, amylopectin), beta-1, 4-chitosan, beta-1, 4-N-acetyl chitosan (chitin), beta-1, 4-mannan, beta-1, 4-xylan, an inulin, curdlan, etc.

[0006] Although the number average degree of polymerization (the number of averages of the pyranose ring contained in a monad or a furanose ring) of these polysaccharides is ten or more preferably an upper limit does not have it five or more it is desirable in the ease of handling that it is 500 or less.

[0007] ** [the carbamoyl group which accomplishes the carbamate derivative of the polysaccharide of this invention does not have 80% of all the hydroxyl groups that are shown by the above-mentioned general formula (1) and correspond and that a polysaccharide has] The 20 remaining% which is that in which 100% forms this carbamoyl group and the urethane bond thru/or 0%, although it is generally still a hydroxyl group, it is convertible for a substituent besides a part.

[0008] General formula (1) In the radical expressed, R1, R2, R3, and R4 and R5 are a *** atom or a carbon number 1 thru/or eight alkyl groups, or a halogen atom, respectively. At least two of R1-R5 are a carbon number 1 thru/or the alkyl group of 8, or a halogen atom, and it is a different substituent, and at least one of R1-R5 is a carbon number 1 thru/or the alkyl group of 8 especially preferably, and at least one is a halogen atom. As a carbon number 1 thru/or eight alkyl groups, a methyl group, a ethyl group, a propyl group, butyl, a hexyl group, an octyl radical, etc. are mentioned, and a chlorine atom, a bromine atom, an iodine atom, etc. are mentioned as a halogen atom.

[0009] The reaction which produces urethane from usual alcohol and isocyanate is applicable to composition of the carbamate derivative in connection with this invention as it is. For example, it can obtain by making corresponding isocyanate and a corresponding polysaccharide react in a suitable solvent by making Lewis acid, such as Lewis bases, such as the third class amine, or a tin compound, into a catalyst. Moreover, composition of isocyanate is easily compoundable by, for example, making a phosgene act on the amino group of a corresponding aniline derivative.

[0010] The polysaccharide carbamate derivative of this invention is the matter very useful as a functional material, and is especially useful as a separating medium for optical resolution. It is also possible to support on the film otherwise and to carry out membrane separation by making the polysaccharide carbamate derivative of this invention into a separating medium, although it is common to use chromatography methods, such as a gas chromatography, liquid chromatography, thin-layer chromatography, and supercritical chromatography, in order to use it for the purpose which separates a compound and an optical isomer.

[0011] Although the method of forming a capillary tube and using the wall by the approach of filling up a column as fine particles, the approach of coating a capillary column, and this separating medium etc. is taken in order to apply to a liquid chromatography method by making the polysaccharide carbamate derivative of this invention into a separating medium, considering as fine particles is common, although the magnitude of a particle with desirable making into the shape of a bead whether to grind this changes with magnitude of the column to be used in order to make this separating medium into fine particles — 1 micrometer — 10mm — it is — desirable — 1 micrometer — 300 mm it is — as for a particle, it is desirable that it is porosity.

[0012] Furthermore, it is desirable to make this separating medium hold to support for

improvement in the proof-pressure capacity of a separating medium, swelling by the solvent permission, prevention of contraction, and improvement in the theoretical plate number. although the magnitude of support changes with the magnitude of the column to be used or a plate — general — 1 micrometer — 10mm — it is — desirable — 1 micrometer — 300 mm it is — support is porosity — desirable — an average aperture — 10A—100 nm it is — it is 50A—50000 ** preferably. The amount which makes this separating medium hold is 5 — 50 % of the weight preferably one to 100% of the weight to support.

[0013] As an approach of making support supporting a polysaccharide derivative, the chemical approach or a physical method may be used. In case a polysaccharide is derivatized as a chemical approach, some hydroxyl groups are protected, after derivatization, deprotection is carried out and there is a method of combining this and silica gel chemically (Y.Ohamoto et al., J.Liq.Chromatogr., 10 (8&9), 1613, 1987). as a physical method, a polysaccharide derivative is dissolved in the solvent of fusibility — making — support — good — mixing — warming under reduced pressure — there is a method of making a solvent distill off by the bottom or the bottom of an air current etc.

[0014] As support, there is porous organic support or porous inorganic support, and it is porous inorganic support preferably. The high polymer which a thing suitable as porous organic support becomes from polystyrene, polyacrylamide, polyacrylate, etc. is mentioned. The composition or the natural matter like a silica, an alumina, a magnesia, titan oxide, glass, a silicate, and a kaolin is mentioned, and a thing suitable as porous inorganic support has silanizing processing using the organic silane compound as the approach of surface treatment, a surface treatment method by the plasma polymerization, etc. for performing surface treatment, in order to improve compatibility with a polysaccharide derivative.

[0015] Although there is no constraint if a reactant liquid is removed when there is especially no constraint as an eluate in the case of performing liquid chromatography except for the dissolution or this, and the liquid that reacts about this separating medium and this separating medium is combined with support by the chemical approach, mixed solutions, such as n-hexane, various alcohol, and a tetrahydrofuran, are used preferably. Moreover, since the separation property of a compound or an optical isomer may change with eluates, it is desirable to examine the separation property by the mixing ratio of various solvents.

[0016] case where thin-layer chromatography is performed on the other hand 0.1 micrometers — 0.1mm Thickness which consists of a little binder with this separating medium that consists of a particle of extent if required 0.1—100mm What is necessary is just to form a layer in the shape of a support plate. Moreover, in performing membrane separation, it uses as a hollow filament or a film.

[0017] [Effect of the Invention] The separating medium which makes an active principle the polysaccharide carbamate derivative which has the aromatic series radical which has two or more kinds of different substituents of this invention is effective in separation of various compounds, and its separation is very effective especially in separation of the very difficult optical isomer conventionally. The either is stronger and the optical isomer which is the object of separation is adsorbed by this separating medium. Especially this separating medium tends to change the separation of a separating medium which consists of derivative which has a non-substitution product, one corresponding substitution product, or the two same corresponding substituents, and an adsorption property by the substituent, and tends to raise the effectiveness of separation made into the purpose, especially the effectiveness of optical resolution.

[0018] Although relation of the remarkable change and the remarkable substituent of such a separation property cannot be explained completely, a substituent is considered [which giving change and the substituent itself have in the form of a molecule] that the physical and electronic effect which chemical property (polarizability, hydrogen bond nature, polarity, etc.) and a substituent have on the pi-electronic system of an aromatic series ring combines intricately. It became clear to have very effective effect, when a substituent embellishes the separation property, of a separating medium by this invention, and the development of the separating medium which has various kinds of properties of it was attained.

[0019] [Example] It cannot be overemphasized that it is not that by which this invention is limited to these hereafter although an example explains this invention concretely. In addition, parameter k' and alpha which are used in an example are defined as follows.

[0020] [Equation 1]

$$k' (\text{客観値}) = \frac{\text{ある光学異性体の保持時間} - \text{テッタタイム}}{\text{テッタタイム}}$$

α (アーチカル) = より強く吸着される光学異性体の k'

[0021] Synthetic microcrystalline cellulose of synthetic example-1 cellulose tris (3-methyl-4-chlorophenyl carbamate) (Merck Co. make), 1.0 g, pyridine 50ml, 3-methyl-4-chlorophenyl isocyanate 9.3g After heating at 100 degrees C for 17 hours, the methanol (500ml) was filled with the reaction mixture. The produced precipitate was dried the RO exception and cellulose tris (3-methyl-4-chlorophenyl carbamate) was obtained. The elemental-analysis value of the cellulose tris (3-methyl-4-chlorophenyl carbamate) obtained the yield of 3.48g is shown below, calculated value C and 54.33%, H and 3.92%, N, 6.34%; Cl, 16.08% actual measurement C, 53.27%, H, 4.24%; N, 6.28%; Cl and cellulose tris (3-methyl-4-chlorophenyl carbamate) 1.0g obtained in the example -1 of 15.65% examples-1 composition N,N-dimethylacetamide (10ml) It dissolved, and, in addition, distilled off under reduced pressure of a solvent each time in 2 steps to silica gel (DAISO Co., Ltd. make, die sow gel (1000 micrometers of apertures)) 4.0g which processed this by 3-aminopropyl ethoxy silane, and the bulking agent was prepared.

[0022] The silica bead which supported the cellulose tris (3-methyl-4-chlorophenyl carbamate) obtained in the application -1 example -1 was filled up with the slurry method which used the hexane-liquid paraffin (2:1) for the stainless steel column with a die length [of 25cm], and a bore of 0.46cm. Gulliver UV970 was used for Gulliver PU980 by Jasco Industries, and a detector at the high-speed liquid chromatograph machine. The result of having divided various racemic modification was shown in Table 1.

[0023] Synthetic microcrystalline cellulose of synthetic example-2 cellulose tris (3-chloro-4-methylphenyl carbamate) (Merck Co. make) 1.0 g, pyridine 50ml, 3-chloro-4-methylphenyl isocyanate 9.3g After heating at 100 degrees C for 17 hours, the methanol (500ml) was filled with the reaction mixture. The produced precipitate was dried the RO exception and cellulose tris (3-chloro-4-methylphenyl carbamate) was obtained. The elemental-analysis value of the cellulose tris (3-chloro-4-methylphenyl carbamate) obtained the yield of 3.42g is shown below, calculated value C and 54.33%, H and 3.92%, N, 6.34%; Cl, 16.08% actual measurement C, 53.14%; H, 4.23%; N, 6.22%; Cl and cellulose tris (3-chloro-4-methylphenyl carbamate) 1.0g obtained in the example -2 of 15.96% examples-2 composition N,N-dimethylacetamide (10ml) Silica gel which dissolved and processed this by 3-aminopropyl ethoxy silane (the Merck Co. make, LChrosper S14000) In addition, it distilled off under reduced pressure of a solvent each time in 2 steps to 4.0 g, and the bulking agent was prepared.

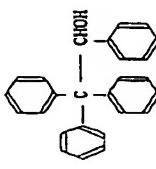
[0024] The silica bead which supported the cellulose tris (3-chloro-4-methylphenyl carbamate) obtained in the application -2 example -2 was filled up with the slurry method which used the hexane-liquid paraffin (2:1) for the stainless steel column with a die length [of 25cm], and a bore of 0.46cm. Gulliver UV970 was used for Gulliver PU980 by Jasco Industries, and a detector at the high-speed liquid chromatograph machine. The result of having divided various racemic modification was shown in Table 1.

[0025] In order to clarify the -one example effect of the invention of a comparison, the separating medium which made the active principle the cellulose tris (3, 5-dimethylphenyl carbamate) derivative as a comparison article was produced, and the result of the optical resolution to the various racemic modification was shown in Table 1.

[0026]

[Table 1] ラセミ体の光学分割実験結果

ラセミ体	実施例1		実施例2		比較例1	
	k'	a	k'	a	k'	a
トランスキードルペニ 0 Ph	0.43(+)	3.25	0.45(+)	2.09	0.74(-)	1.68
1,2,2,2-テトラフェニル エタノール	0.73(+)	3.05	0.65(+)	1.95	1.37(+)	1.34



[Translation done.]

〔00006〕これら多種の平均屈筋度（一分子中に含まれるビラノース環又はフランノース環の平均数）は5以下であることをが取引の容易さにおいて好ましい。〔00007〕本標準の多糖のカルボメート結合率を求める方法は上記の一概式(1)で示され、対応するカルボメイル基は上記の一概式(1)で示され、対応するカルボメイル基とウレタン結合を用いて成していものである、ウレタン結合の割合は約90%であるが、残りの約10%は一般に水溶性のままであるが、〔00008〕一概式(1)で置換する際において、R₁

による表面処理法等がある。

【0-1-5】 依然はクロマトグラフィーを行なう場合溶媒を除いて、該分離法を専門的ではこれと反対する液体として特に適切ではなく、またその分離能を化学的方法で粗体に結合した場合には反応活性体を保つては制約せないが、好ましくはヘキサン、各種アルコール、テトラヒドロフランなどの混合溶媒が用いられる。また、溶被液によつて化合物または光学異性体は変化するところがあるので注意を要する。

【0-1-6】 一方、薄層クロマトグラフィーを行う場合はには 0.1% ～ 1% の程度の性子からなる板分離剤と、必要であれば少量の結合剤より成る原液 0.1 ～ 100 μl の層を支持板状に形成すれば良い。また距離を取る場合には支持板状あるいはフィルムとして用いる。

【0-1-7】 [光学の効率] 本説明の二重鏡以上の異なる選択換算を有する場合の効率である。

(10-12) 更に分離剤の耐圧能力の向上、溶融樹脂による遮蔽、吸盤の防止、理論剪断の向上のために、粘着剤を相手に保持させることが好ましい。相手の大きさは使用するカラムやプレートの大きさにより異なるが、一般に 100μ ～ 1000μ であり、好ましくは 50μ ～ 50000μ である。一方で、相手は多孔質であることが好ましく、平均孔径は 10μ ～ 100μ であり、好ましくは 50μ ～ 5000μ である。また、分離剤を保持させる量は相手に対して $1 \sim 100$ 倍である。好ましくは 50μ ～ 5000μ である。

(10-13) 多孔質保持は相手とともによい。化学的な方法などは生物学的の方法でも物理的な方法でもよい。

しては多糖を酵素化する際に一部の水酸基を保護しておき、精製化後、脂保護し、これどシリカゲルなどを用いて分別するという方法がある (Y. Okamoto et al., J. Lit. Chromatogr., 10 (Aug. & Sept.), 1613, 1987)。物的現象としては、多糖構造を可溶性の溶浴に溶解させ、担体と良く混和し、減圧下、加温下または気流により溶剤を留去させる方法などがある。

(0.014) カゼイは、多孔性担体生体では多孔性無機担体である。ポリスチレン、ガラス等の有孔性担体として適当なもの、ポリアクリルアミド、ポリアクリレートなどからなる高分子が挙げられる。多孔性無機担体として適当なもののうち、アルミニナ、マグネシア、酸化チタン、ガラスケイ酸塩、カオリナイト等が挙げられる。カオリナイトのうち合成もしくは、天然のカオリナイトに表面処理を施して半導体表面処理の方法としては半導体物質が吸着し、アラブマイト化物を用いたシリコン化物を用いたシリコン化物や、アラブマイト化物に表面処理を施して半導体表面処理の方法としては半導体物質が吸着する。

α (分離係数)	$=$	より強く吸着される光学異性体の k'	より弱く吸着される光学異性体の k'
[0021] 合成例-1			
セルローストリス (3-メチル-4-クロロフェニルカルバメート) の合成	20	した。	
微結晶性セルロース (マルク社製) 1.0g、ビリジン50ml、3-メチル-4-クロロフェニルソシアナート9.3gを100°Cで1時間加熱した後、反応混合物をメタノール (500ml) に注ぎた。生じた沈殿をロ過、乾燥し、セルローストリス (3-メチル-4-クロロフェニルカルバメート) を得た。収量3.48g (34.8%)	20	合成例-2 セルローストリス (3-メチル-4-クロロフェニルカルバメート) の合成	した。
得られたセルローストリス (3-メチル-4-クロロフェニルカルバメート) の元素分析値を以下に示す。	30	セルローストリス (3-クロロ-4-メチルフェニルカルバメート) を得た。収量3.42g	得られたセルローストリス (3-クロロ-4-メチルフェニルカルバメート) の元素分析値を以下に示す。
計算値 C: 54.33%; H: 3.92%; N: 6.34%; Cl: 1.08%	6.08%	セルローストリス (3-クロロ-4-メチルフェニルカルバメート) の元素分析値を以下に示す。	計算値 C: 54.33%; H: 3.92%; N: 6.34%; Cl: 1.08%
実測値 C: 53.27%; H: 4.24%; N: 6.28%; Cl: 1.09%	6.09%	セルローストリス (3-クロロ-4-メチルフェニルカルバメート) の元素分析値を以下に示す。	計算値 C: 54.33%; H: 3.92%; N: 6.34%; Cl: 1.09%

実験例 1-1 得たセルローストリス（3-メチル-4-クロロフェニルカルバメート）1.0gをN,N-ジメチルアセトアミド（10ml）に溶解し、これを3-アミノプロピルエトキシジランで処理したシリカゲル（ダイマー社製、ダイソーグル（孔径1000μm）4.0gに2回に分けて加え、その都度溶液を減圧下で留去し、充填剤を調製した。

【0.012】使用例-1
実験例 1-1 得たセルローストリス（3-メチル-4-クロロフェニルカルバメート）のステンレスカラムにヘキサン-1-ブロム（2.0 ml）を注入したスラリーにて充填した。充填後はクロマトグラフ槽にて分子量標準物質のGalliver, Pluron、検出器にはGalliver 19970を用いた。種々のセラミクスを分別した結果を表に示す。

した。
〔0025〕比較例1
注明の効果を明らかにするため、比較としてセリロ
ーストリス(3,5-ジメチルフェニルカーボネート)系
ラセミ体の光学分割実験結果

〔0026〕
〔実験例1〕
ラセミ体の光学分割実験結果

ラセミ体	実験例1			実験例2			比較例1		
	k'	α	k'	α	k'	α	k'	α	
トランスクチルベン オキシド	0.43(+)		3.25	0.45(+)	2.09	0.74(-)	1.68		
									
1,2,2,2-テトラフェニル エタノール	0.73(+)	3.05	0.65(+)	1.95	1.37(+)	1.34			
